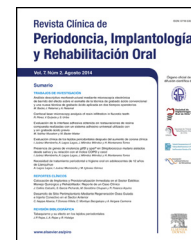




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### REVIEW ARTICLE

## Some aspects of bone remodeling around dental implants

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### KEYWORDS

Dental implants;  
Bone remodeling;  
Osteoclast;  
Osteoblast

**Abstract** Considering that success of dental implants is not only related to osseointegration, but also with their survival rates, the aim of this study was to perform a literature review about bone remodeling around osseointegrated implants. A detailed search strategy was used for this, and articles published between the years 1930 and 2012 were selected. The rare data found in the literature demonstrated that implants are osseointegrated 30 days after their placement. However, active bone remodeling with osteoclasts and osteoblasts working in synchrony continues to occur. Therefore, after osseointegration, the initially formed bone, which presents characteristics of spongy bone, is gradually resorbed and replaced by compact bone after 90 days. Furthermore, other portions of bone tissue a little more distant from the interface, which establish direct contact with the implant, are also damaged during the drilling process, and therefore, they also need to be remodeled. Among the rare studies found in the literature about bone remodeling after osseointegration, there were no verified studies on the possible influence of implant surface treatments on bone remodeling that occurs after osseointegration. Only studies involving implants with machined surfaces have been conducted up to now.

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## PALABRAS CLAVE

Implantes Dentales;  
Remodelación Ósea;  
Osteoclastos;  
Osteoblastos

## Consideraciones con respecto remodelación ósea alrededor de los implantes dentales

**Resumen** Teniendo en cuenta que el éxito de los implantes no solo se asocia a su osteointegración, sino también a su tasa de supervivencia, en otras palabras, a la permanencia de los mismos, en función, a largo plazo, el presente artículo tiene como objetivo realizar una revisión bibliográfica acerca de la remodelación ósea alrededor de los implantes dentales. Se utilizó una estrategia de búsqueda detallada, y se seleccionaron los artículos publicados entre los años 1930 y 2012. Los pocos datos en la literatura muestran que en las ratas los implantes osteointegrados se presentan después de 30 días de su instalación. Sin embargo, una remodelación ósea activa por los osteoclastos y los osteoblastos que trabajan sincrónicamente sigue ocurriendo, de manera que después de la osteointegración, el hueso formado inicialmente, que presenta características de hueso esponjoso, se reabsorbe y se sustituye por hueso compacto después de 90 días gradualmente. Además, otras porciones de tejido óseo un poco más distantes de la interfaz, que establecen contacto directo con el implante, también se dañan durante el proceso de perforación antes de la implantación, y por lo tanto, también necesitan ser remodeladas. Entre los pocos estudios en la literatura sobre el remodelado después de la osteointegración no hay estudios sobre una posible influencia de los tratamientos de superficie del implante en la remodelación ósea que ocurre después de la osteointegración. Hasta ahora solo se han realizado estudios con implantes con superficies mecanizadas.

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## Introduction

Bone, a type of connective tissue, presents cells, and in spite of being mineralized, it is constantly renewed by means of the bone remodeling process. This process is characterized by bone resorption by osteoclasts, followed by bone formation by osteoblasts.<sup>1</sup> Diverse studies have demonstrated the relevance of bone remodeling to tissue responses that guarantee osseointegration,<sup>2-6</sup> which is defined as the direct structural and functional connection between the organized vital bone and the surface of a titanium implant, capable of receiving functional loads.<sup>7-9</sup>

The success of implants is associated first with their osseointegration, and later on with their survival rate; that is to say, their long term permanence in function. Although there are several studies involving osseointegration of dental and/or orthopedic implants, the majority of the investigations have elucidated the tissue responses that constitute the initial process of bone-implant integration.<sup>2,10-14</sup>

Considering that the remodeling process is continuous, it may be of relevance not only to osseointegration, but also to the longevity of dental implants. Therefore, the purpose of this study was to conduct a review of the literature with a view of elucidating the events associated with bone remodeling after the osseointegration of implants. In addition, it was also performed a search to data with respect to a possible influence of treatments for modifying implant surfaces on these same events.

## Materials and methods

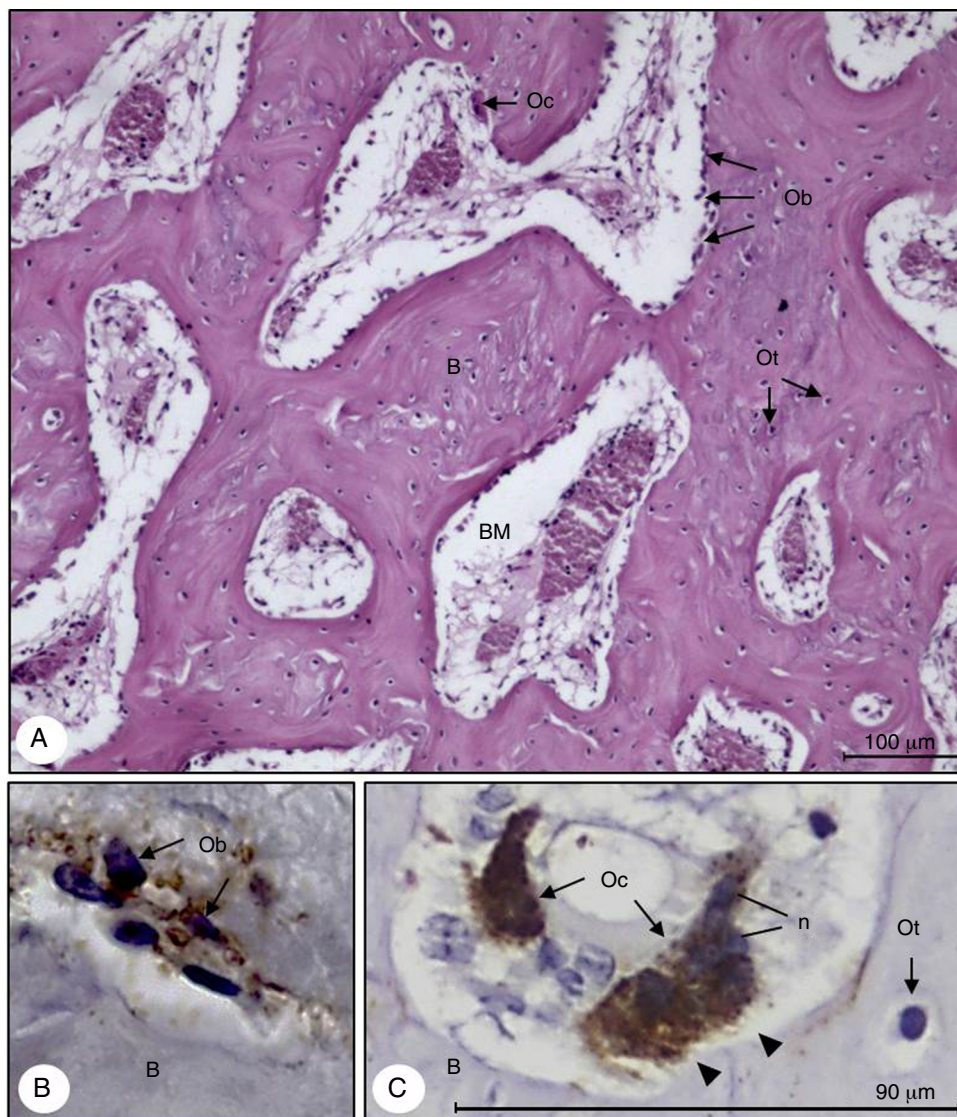
In order to conduct this literature review a detailed search strategy was used in various data bases, between

the years 1930 and 2012. The following descriptors were used: "Osseointegrated Implant", "Bone remodeling", "Osteoclast", "Osteoblast" and "Surface treatments". The inclusion criteria were systematic review studies, meta-analyses, conventional reviews of the literature, controlled and randomized case studies, non-randomized clinical cases and articles of opinion, with an approach to the above-mentioned uniterms. Studies that were not written in the Portuguese and English languages were excluded. After critical analysis of the bibliography surveyed, the suitable articles were selected. The data obtained were carefully analyzed and correlated for discussion of the results pointed out in the literature.

## Literature review

### Considerations about bone tissue and the process of bone remodeling

Bone, a connective tissue, has cells, and in spite of presenting the particularity of being mineralized, it is constantly renewed by means of the bone remodeling process.<sup>1</sup> In clinical terms, the rate of bone remodeling, also denominated bone turnover, is the period necessary for new bone to replace the existent bone, guaranteeing adaptation of the neoformed bone to its microenvironment.<sup>15</sup> Microscopically, bone remodeling consist in bone resorption by osteoclasts, followed by bone formation by osteoblasts<sup>16,17</sup> (Fig. 1). Both cells may be characterized by morphological and biochemical aspects. Osteoclasts, formed by the fusion of mononucleated cells of the hematopoietic lineage,<sup>18,19</sup> are multinucleated giant cells that degrade the mineralized bone matrix. They are located in excavation on the bone surface,



**Figure 1** Light micrographs of portions of tibiae which were surrounding the implants. (1A) Several bone trabeculae (B) and bone marrow regions (BM) are observed. Osteoblasts (Ob) and osteoclasts (Oc) are located on bone surface, whereas osteocytes (Ot) are located inside the bone matrix (B). H&E. Bar: 100 µm. (1B) Osteoblasts (Ob), located on bone surface (B), show alkaline phosphatase (ALP)-positive cytoplasm (brown-yellow color). Immunohistochemistry for detection of ALP (osteoblast marker) counterstained with Hematoxylin. Bar: 30 µm. (1C) Giant multinucleated osteoclasts (Oc) exhibiting intense TRAP-positivity in the cytoplasm (brown color) are observed. n: nuclei. Ot: osteocytes. Arrowheads: Howship lacunae. Immunohistochemistry for detection of TRAP (osteoclast marker) counterstained with Hematoxylin. Bar: 90 µm.

denominated Howship lacunae.<sup>16,20,21</sup> In their cytoplasm, osteoclasts present the enzyme acid phosphatase, which may be distinguished from the other isoenzymes because it is resistant to inhibition by tartaric acid, thus denominated tartrate resistant acid phosphatase (TRAP).<sup>4,29</sup> In addition to TRAP, the osteoclasts also synthesize other enzymes, such as metalloproteinase-9 (MMP-9) and cathepsin K.<sup>22</sup>

On the other hand, the osteoblasts, cells originating from precursors of mesenchymal origin, are mononucleated, smaller in size than osteoclasts and related to the production and mineralization of bone tissue matrix. They are disposed in a continuous layer on the surface of the bone matrix. Osteoblasts and pre-osteoblasts exhibit high levels of alkaline phosphatase enzyme (ALP) on the surface of

their cytoplasmic membranes which, when released, contribute to the initiation of mineralization and progressive growth of hydroxyapatite crystals. In the initial process of bone tissue formation, after the osteoblasts have secreted the first layer of organic matrix, they appear to assume an important role in its mineralization. From the osteoblasts adjacent to the recently synthesized organic bone matrix, small vesicles emerge. ALP belongs to a family of enzymes that hydrolyze phosphate ions, supplying them to the interior of the vesicles. An increase in the concentration of calcium ions inside these vesicles also occurs, probably through the phospholipids in their membranes. Thus a supersaturation of phosphate and calcium occurs, resulting in the precipitation of phosphate and calcium inside the vesicles.



Afterwards, there is vesicle membranes rupture and mineralization spreads throughout the matrix. This process is characteristic of the sites in which bone tissue formation and mineralization is occurring. Thus, ALP contributes to the beginning of mineralization and progressive growth of hydroxyapatite crystals of bone matrix.<sup>21,23</sup> In this context of tissue renewal, the periosteum may be included, because it is an important source of osteogenic cells. It is made up of two layers: An external layer of fibrous conjunctive tissue, in which there are few cells and vessels, and an internal layer, that has osteoprogenitor mesenchymal stem cells, and a vast network of blood vessels in direct contact with the bone.<sup>2,24</sup>

As bone matrix is produced, some osteoblasts become trapped within its lacunae, and begin to exhibit cytoplasmic extensions, which are found inside the bone canaliculi. These extensions go toward to the extensions of adjacent osteocytes, and in the direction of other cells. Then, gap junctions which allow intercellular communications are established between osteocytes/osteocytes and osteocytes/other bone cells. The junctional communications enable even the osteocytes located in the deepest regions of bone to respond to systemic changes, and modifications on the bone surface. Therefore, osteocytes constitute a complex network that interconnects the bone surface with the most internal portions, and are responsible for the maintenance and vitality of the bone matrix.<sup>21,23</sup> In addition, the osteocytes are considered essential for bone remodeling, and it has been demonstrated that apoptosis of this cell appears to stimulate the resorptive activity of osteoclasts.<sup>25</sup> Osteoclasts be responsible for the phagocytosis of these osteocytes, thereby avoid triggering an inflammatory process within bone tissue.<sup>26-28</sup>

### Osseointegration and bone remodeling around osseointegrated implants

In the 1960s, the Swedish orthopedist Branemark and his collaborators discovered, by chance, the occurrence of bone integration with titanium, denominated osseointegration. Thus, osseointegration consists of the clinically asymptomatic, rigid fixation of alloplastic materials, maintained during functional loads.<sup>7</sup>

In rats, osseointegration is acquired around 1 month after implants placement,<sup>3</sup> and is characterized by the coverage of the implant threads by the adjacent bone tissue, in addition to the presence of insignificant inflammation and absence of fibrous tissue.<sup>3,5,12</sup> A suitable model for this type of study was introduced in 1998, using the rat maxilla for observation of the tissues responsible for titanium implantation from 1 to 30 days after insertion of the implant. In this study, it was observed that the appearance of neoformed bone tissue occurred on the fifth day after implant placement, and covered the entire implant 30 days after osseointegration. However, concomitant with osseointegration, damaged bone was observed, exhibiting lacunae of empty osteocytes, or osteocytes with a picnotic appearance between the pre-existent and neoformed bone around the implants.<sup>3,5,12</sup> Considering that the remodeling process is continuous, it may be of relevance with respect not only to osseointegration, but also to the longevity of dental implants, the purpose of this study was to conduct

a review of the literature with a view to elucidating the events associated with bone remodeling after the osseointegration of implants. In addition, it was performed a search to investigate the existence of data with respect to a possible influence of treatments for modifying implant surfaces on these same events. A long term study investigating the response to bone tissue present around titanium implants that had become osseointegrated in rats, was conducted by Haga et al.<sup>29</sup> These authors showed by means of active bone remodeling, with osteoclasts and osteoblasts working in synchrony, the bone initially formed around the implant, which presents characteristics of spongy bone, is gradually resorbed until it disappears at the end of 90 days, when it is completely replaced by compact bone. The morphological and biochemical alterations associated with the bone remodeling process, which occur around machined implants from 1 to 3.5 months after osseointegration are illustrated in Fig. 2.<sup>29</sup>

#### One month after implant placement

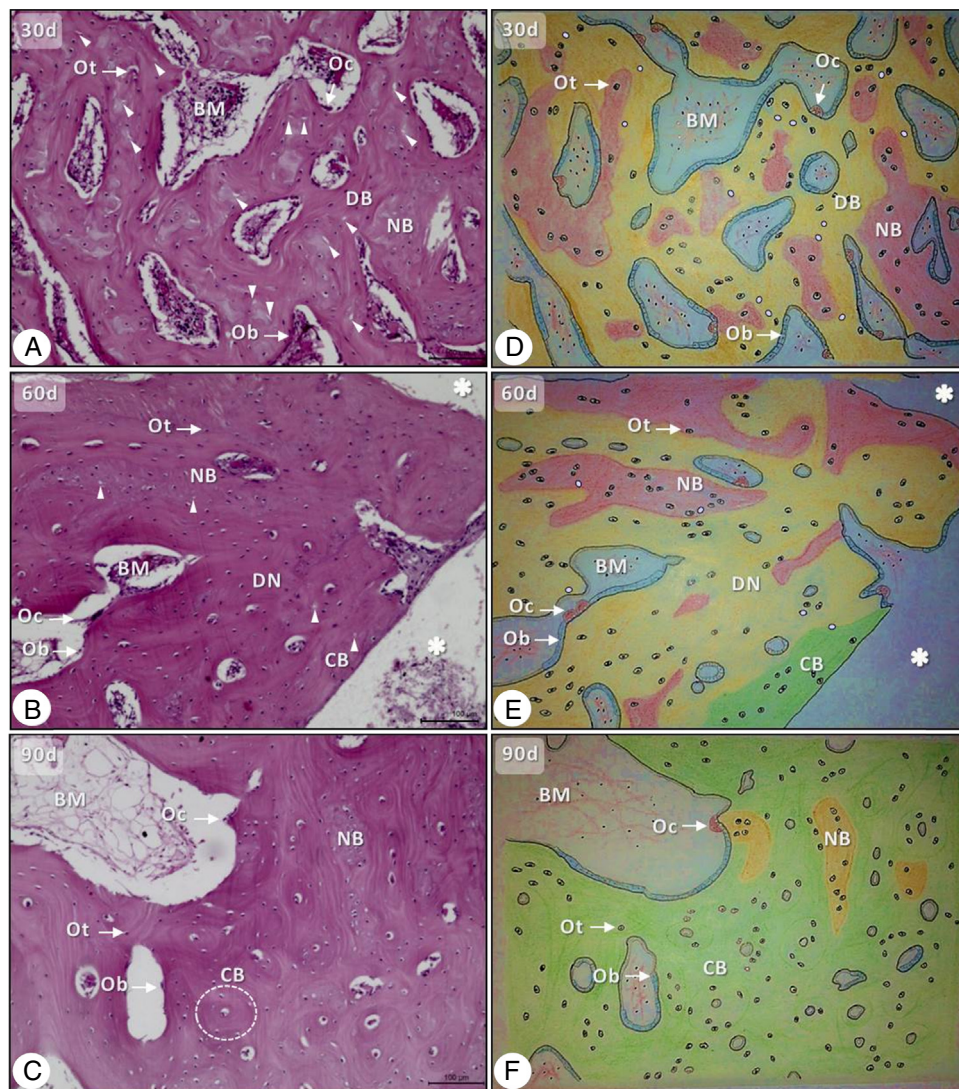
Osseointegration is observed in all the surfaces of the implants.<sup>3,29</sup> There is a thin layer of neoformed bone present on the implant surface. However, a part of this surface is shown not to be in contact with the neoformed bone. In these areas, medullary spaces containing small blood capillaries are shown to be in contact with the implant surface. The neoformed bone contains osteocytic lacunae exhibiting intact osteocytes. In the region of pre-existent bone, a cement line is easily identified beyond the empty osteocytic lacunae. The double markings of TRAP and ALP enzymes for the detection of osteoclasts and osteoblasts, respectively, show positivity for both cells on the neoformed bone surface. ALP-positive osteoblasts are found close to the area occupied by TRAP-positive osteoclasts, suggesting the occurrence of synchrony and equivalence of the activity of these cells, and therefore, of bone remodeling.<sup>29</sup>

#### From 1.5 to 2.5 months after the placement of implants

The formation of bone tissue proceeds in the direction of the damaged bone containing empty osteocytic lacunae, resulting in a reduction in it. Practically the entire implant surface is covered by neoformed bone. The portion of neoformed bone exhibits characteristics of spongy bone. Some empty osteocytic lacunae remain, however, the area containing this type of structure is shown to be smaller. There is the presence of an evident cementing line between the pre-existent bone (containing empty osteocytic lacunae) and the neoformed bone. A lower number of ALP-positive osteoblasts and TRAP-positive osteoclasts are observed. In addition, both cell types present reduced volumes, suggesting less cell activity.<sup>29</sup>

#### Three months after implant placement

There is the absence of empty osteocytic lacunae. The area of pre-existent bone has been replaced by neoformed bone containing intact osteocytes. The neoformed bone presents the morphological characteristics of compact bone. There are only some capillaries found between the implant and neoformed bone. ALP-positive osteoblasts and TRAP-positive osteoclasts are rarely observed around the implants, except in the bone marrow regions.



**Figure 2** Light micrographs showing morphological changes in the surrounding bone around implants at 1, 2 and 3 months after osseointegration (2A–2C). Bar: 100  $\mu$ m. The schematic representation of each light micrograph summarizes the main histological events in the replacement of the injured bone by newly formed bone (2D–2F). (2A, 2D): One month (30 days) after implant osseointegration, woven bone and bone marrow regions (BM) are observed in the light micrograph. Many osteoblasts (Ob) and osteoclasts (Oc) are located on bone surface. It can be found many regions of newly formed bone (NB), which are represented in pink color in the scheme. Inside the bone matrix, several osteocytes (Ot) are observed. However, empty osteocytes lacunae are still observed (white color), mainly in the regions of damaged bone (DB), in yellow color. (2B, 2E): Two months (60 days) post-osseointegration, the woven bone seems to reduce in volume when compared with 1-month period. Moreover, the woven bone previously in contact with the implant is being replaced by cortical. (2C, 2F): Three months (90 days) post-osseointegration, the woven bone seems to be completely replaced by cortical bone. The woven bone previously in contact with the implant is being replaced by cortical bone.

In the period comprised between 3 and 3.5 months after acquisition of osseointegration, minimal morphological and biochemical changes are related, such as for example, a slight increase in neoformed bone thickness (with its corticalization proceeding for up to 12 months after osseointegration).

The distribution and density of ALP-positive osteoblasts and TRAP-positive osteoclasts, and the distance between the cementing lines are identical to those observed in the period of 3 months after implant placement. Once again it is important to emphasize that the neoformed bone undergoes gradual changes from spongy to compact bone due to

its continuous remodeling. However, it exhibits the same biological properties as intact bone after osseointegration is acquired.<sup>29</sup>

### Implant surface treatments and bone remodeling after acquisition of osseointegration

Commercially pure titanium (cpTi), biocompatible material, shows no biological properties of osteoinduction or osteogenesis. For this reason, various surface treatments of titanium implants have been proposed, and carefully

investigated. These studies have allowed one to observe that the process of osseointegration is favored by surface treatments, both in terms of duration of the events associated with complete osseointegration and in situation of unfavorable bone quantity and quality.<sup>30,47</sup> The biological logic of these treatments is to make this microenvironment as similar as possible to the bone microenvironment, making the implant surface mimic the morphology and composition of the constituents of bone tissue itself.<sup>30,31,47</sup>

The process of changing the cpTi surface may be performed by the techniques of subtraction, particle adhesion or by association of both.<sup>31</sup>

The treatments of subtraction consist of removal of portions of the implant surface. An example of subtraction treatment is irradiation of the implant surface with a LASER beam. This process results in an increase in resistance to corrosion and biocompatibility of titanium, due to its oxidation and subsequent formation of oxides and nitrides.<sup>32</sup> Moreover, irradiation with LASER joins advantages characteristics, such as non-contamination of the surface and a high degree of reproducibility of this technique, which produces a complex and homogeneous surface morphology, with a high degree of purity, thus favoring osseointegration and increasing the removal torque.<sup>30,32-34</sup> In addition to these techniques, treatments with acids either associated with airborne particle abrasion with titanium oxide – TiO<sub>2</sub> or aluminum oxide – Al<sub>2</sub>O<sub>3</sub>,<sup>35</sup> or not, are also forms of subtraction techniques.

As opposed to subtraction treatments, addition treatments consist of the addition of substances to the implant surface, such as, for example, the incorporation of ceramics such as hydroxyapatite (HA) [Ca<sub>10</sub>(PO<sub>4</sub>)<sub>6</sub>(OH)<sub>2</sub>].<sup>36</sup> It has been shown that coating implant surfaces with calcium phosphate accelerates osseointegration, especially under conditions of a limited quantity and quality of bone tissue.<sup>37,38</sup> This may be owing to the fact that HA helps to establish an early chemical bond, and consequently, a strong physical chemical interaction with bone in the initial stages of osseointegration. On the implant surface, a layer of apatite hydroxycarbonate is formed, which is chemically and structurally equivalent to the mineral phase of bone, thus a biochemical bond occurs between the implant surface and bone by means of bone matrix deposition on the HA surface. This physical chemical interaction between the collagen of bone and HA of the implant is denominated biointegration. Moreover, greater bone tissue formation is observed around implants coated with HA, than in cpTi implants.<sup>39</sup>

When materials such as HA, considered bioactive, are in contact with the live tissue, they undergo superficial dissolution induced by cell activity, releasing calcium and phosphorous ions into the extracellular medium. These ions are incorporated into the microcrystals of HA of the bone; that is to say, bone matrix is deposited on the HA surface, leading to biointegration.<sup>40</sup> Furthermore, HA is commonly used for coating metal implants, due to the mechanical advantages of metals added to the excellent biocompatibility and bioactivity of HA. This association (cpTi and HA) provides an increase in the strength of the interface with bone tissue.<sup>30,41-43</sup> Methods of chemical deposition of HA have been studied to improve the bond of the coating to the implant surface. Among these, there is emphasis on the biomimetic method, which mimics the body's

biological process of hard tissue formation and consists of immersion of the substrate to be coated in a synthetic solution denominated simulated body fluid solution (SBF)<sup>36</sup> and was performed by Queiroz et al.<sup>30</sup> SBF has chemical composition, temperature and pH that simulate blood plasma.

The implant surface treatment methods may also be classified according to the topographic characteristics they give implants. Implant surface topography varies according to the method by which it is obtained; that is to say, by means of macro, micro or nanotechnology.<sup>14,30,34,44</sup>

By means of implant surface treatments greater implant surface roughness may be obtained. Roughness represents a micro or nanomorphological structural modification that provides an increase in the area of contact between the bone and implant.<sup>6</sup> One is able to distinguish between macroroughness (100 μm to millimeters), microroughness (100 nm–100 μm) e nanoroughness (less than 100 nm).<sup>31</sup> Each type of topography has a specific influence on the mechanisms involved in osseointegration. For example, accumulation and organization of the blood clot on the rough surface, create an important physical phenomenon for osteogenesis, such as greater adhesion, proliferation and expression of osteoblast differentiation markers. This leads to an increase in the bone-implant bond strength, and consequently, to success of therapy with implants in the long term.<sup>45-47</sup> Clinical proof of the positive influence of surface treatments on osseointegration is the higher torque required for removal of implants with rough surfaces, when compared with those that have smooth surfaces.<sup>11,48</sup>

cpTi implants modified on a nanometric scale by LASER beam with HA deposition by the biomimetic method, with and without afterwards receiving heat treatment in an oven at 600 °C, favor osseointegration in the periods of evaluation of 30 and 60 days after implant placement in rabbit tibias. Moreover, the surface containing HA that did not undergo heat treatment presented greater biological activity, reducing the time of osseointegration. This latter result is probably associated with the lower degree of crystallinity of hydroxyapatite, which therefore becomes more soluble and similar to biological hydroxyapatite.<sup>30</sup>

In general, the goal of surface treatments is to reduce the time of loading after surgery; accelerate bone growth and maturation to allow immediate loading; increase primary stability; guarantee the success of implants when they are placed in regions that present bone with lower quality and quantity; obtain bone growth directly on the implant surface; obtain the largest possible area of osseointegration; obtain bone-implant contact without the interposition of amorphous protein layers; attract mesenchymal, pre-osteoblastic and osteoblastic cells, in addition to proteins with specific binding to osteogenic cells.<sup>9,44,49,50</sup>

The success of osseointegration, and the maintenance of implants in the long term is dependent on adequate rates of bone remodeling.<sup>44,51</sup> However, up to the present time, we have not found any studies in the literature, which investigate a possible differential effect of these surface treatments of implants on the bone remodeling that occurs after the establishment of osseointegration.



## Discussion

Osseointegration is described as an effective interaction between bone tissue and the implant surface.<sup>7-9</sup> However, damaged bone tissue, with empty osteocytic lacunae, resulting from cutting of the bone for implant placement, remains in the microenvironment around the implant, even after its osseointegration.<sup>29</sup> In the literature, studies with respect to bone remodeling around implants that have already become osseointegrated are rare. Of the articles selected for this review, only one study directly analyzed the events involving renewal of bone tissue in the microenvironment around the implant after osseointegration, in the absence of loads, in an animal model (rats).<sup>29</sup> This study was conducted on the basis of the results obtained by Fuji et al.<sup>3</sup> who demonstrated that this type of investigation could be conducted in animal models (rats) 30 days after the placement of a conventional implant with a machined surface, which was shown to be almost completely covered by bone tissue.

Haga et al.<sup>29</sup> observed that one month after osseointegration, there was still bone tissue around the implant, presenting empty or picnotic osteocytic lacunae. By means of balanced bone remodeling, in which bone resorption by TRAP-positive osteoclasts and bone neoformation by ALP-positive osteoblasts are synchronic and equivalent, the damaged bone is remodeled in a gradual manner and disappears completely 3 months after implantation. Initially, there is replacement of the pre-existent bone, damaged by cutting,<sup>52</sup> by spongy bone, and of this, by compact bone, thus improving the bone quality.<sup>29</sup> These data clearly demonstrated that continual bone remodeling, even after osseointegration is essential for the survival and success of dental implants in the long term.

It is important to emphasize that the studies investigating events associated with bone remodeling after the acquisition of osseointegration, mentioned in this review of the literature, were conducted in the absence of loads.<sup>29</sup> In the presence of loading and depending on the value of the load applied, modifications occur in the bone tissue located around the implant, which must have its structure adequately adapted to receive the forces applied.<sup>53</sup> Furthermore it requires continuous remodeling to replace the regions damaged by fatigue, in order to prevent the occurrence of fractures and loss of the implant.<sup>4,6,54</sup> Therefore, there are higher bone remodeling rates in implants submitted to the action of loads.<sup>6</sup>

In spite of the large number of studies on the topographical, physical and chemical changes on implant surfaces,<sup>14,30,34</sup> up to the present time, we have found no articles in the literature, which have investigated a possible differential effect of these surface treatments on the bone remodeling that occurs after osseointegration has been established.

## Conclusions

It is reasonable to suggest, for example, that bioactive surfaces may continue to be active in the long term, stimulating the bone cells and leading to a higher degree of tissue turnover. On the other hand, it is also possible that the

properties obtained by means of the surface treatments may influence osseointegration only, seeing that at this time the bone cells have greater access to the treated surface.

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## Conflict of interest

No conflicts of interest have been declared.

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